enhance the analgesic potency of the opioid agonist and attenuate the anti-analgesia, hyperalgesia, hyperexcitability, physical dependence and/or tolerance effects of the opioid agonist.

Please replace the fourth paragraph on page 3 with the following new paragraph:

The present invention is also directed to the use of the above-mentioned controlled release formulations for maintenance treatment of previously detoxified opiate addicts.

Please replace the second full paragraph on page 7 with the following new paragraph:

When the controlled release dosage form comprises a transdermal delivery system, the rate of delivery of the opioid agonist will be such that a sufficient mean relative release rate (or flux rate) of the opioid agonist contained in the dosage form is delivered from the transdermal dosage form upon administration. The rate of delivery of the opioid antagonist will be such that an effective amount of the opioid antagonist is delivered to attenuate the anti-analgesia, hyperalgesia, hyperexcitability, physical dependence and/or tolerance effects of the opioid agonist during the intended dosing interval. Preferably, rate of delivery of the opioid antagonist will be such that an effective amount of the opioid antagonist is delivered to enhance the analgesic potency of the opioid analgesic during the dosing interval of the controlled release dosage form. It is not necessary that substantially all of the opioid antagonist be delivered from the controlled release dosage form to meet these goals.

Please replace the first full paragraph on page 8 with the following new paragraph:

The controlled release dosage forms of the present invention preferably deliver the opioid antagonist (e.g., excitatory opioid receptor antagonists) at such a level that the opioid antagonist has selective antagonist action at excitatory, but not inhibitory, opioid receptors. In addition, since the antagonists preferably enhance the analgesic potency of the agonists, the

agonists become effective when administered at reduced doses which would otherwise be subanalgesic. It may be possible to achieve an analgesic effect with 10-100 times lower doses of the (bimodally acting) opioid agonists with the excitatory opioid receptor antagonists of the invention than when the opioid agonist is administered alone. This is because the excitatory opioid receptor antagonists may enhance the analgesic effects of the opioid agonists by attenuating the anti-analgesic excitatory side effects of the opioid agonists. Therefore, in certain preferred embodiments of the invention, the opioid agonist is included in the dosage form and is delivered in an amount which is less than that which has been typically administered for analgesia. In certain embodiments of the invention, the opioid antagonist is delivered such that the amount of opioid agonist included in the dosage form is, e.g., about 10 to about 100 times less than the amount of that opioid agonist typically dosed over the dosing interval.--

a4

Please replace the paragraph bridging pages 10 and 11 with the following new paragraph:

--The excitatory opioid receptor antagonists of the invention are preferably selected from the group consisting of naloxone, naltrexone, diprenorphine, etorphine, dihydroetorphine, pharmaceutically acceptable salts thereof and mixtures thereof. Other opioid antagonists include nalmefene, cyclazacine, levallorphan, pharmaceutically acceptable salts thereof and mixtures thereof. In certain preferred embodiments, the opioid antagonist is naloxone or naltrexone.--

a5

Please replace the paragraph bridging page 16 and 17 with the following new paragraph:

--The controlled release dosage form can be a transdermal patch comprising:
(a) a backing layer which is substantially impervious to said opioid agonist and opioid antagonist; and (b) a polymer matrix layer which is adhered to said backing layer and which has dispersed therein said opioid agonist and opioid antagonist, said polymer being bioacceptable and permitting said opioid agonist and opioid antagonist to be transmitted for transdermal absorption, said opioid agonist and opioid antagonist being stable in said polymer matrix.--

a6

Please replace the third paragraph on page 35 with the following new paragraph:

--For example, a matrix in addition to the opioid agonist and the opioid antagonist, may include hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials. Such matrices may also include digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes, and stearyl alcohol; and polyalkylene glycols. Of these polymers, acrylic polymers, especially Eudragit® RSPO - the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, are preferred. The oral dosage form may contain between 1% and 80% (by weight) of at least one hydrophilic or hydrophobic material. When the hydrophobic material is a hydrocarbon, the hydrocarbon preferably has a melting point of between 25° and 90°C. Of the long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon. In certain embodiments, the oral dosage form contains up to 60% (by weight) of at least one polyalkylene glycol as part of the controlled release matrix.--

a7

IN THE ABSTRACT

Please replace the abstract with the following new abstract:

--Controlled-release dosage forms containing an opioid agonist; an opioid antagonist; and a controlled release material release during a dosing interval an analgesic or sub-analgesic amount of the opioid agonist along with an amount of the opioid antagonist effective to attenuate a side effect of the opioid agonist. The dosage form provides analgesia for at least about 8 hours when administered to human patients. In other embodiments, the dose of antagonist released during the dosing interval enhances the analgesic potency of the opioid agonist.--

a8